Breath Measurements as Volatile Organic Compound Biomarkers

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A brief review of the uses of breath analysis in studies of environmental exposure to volatile organic compounds (VOCs) is provided. The U.S. Environmental Protection Agency's large-scale Total Exposure Assessment Methodology Studies have measured concentrations of 32 target VOCs in the exhaled breath of about 800 residents of various U.S. cities. Since the previous 12-hr integrated personal air exposures to the same chemicals were also measured, the relation between exposure and body burden is illuminated. Another major use of the breath measurements has been to detect unmeasured pathways of exposure; the major impact of active smoking on exposure to benzene and styrene was detected in this way. Following the earlier field studies, a series of chamber studies have provided estimates of several important physiological parameters. Among these are the fraction, f, of the inhaled chemical that is exhaled under steady-state conditions and the residence times, τ_i in several body compartments, which may be associated with the blood (or liver), organs, muscle, and fat. Most of the targeted VOCs appear to have similar residence times of a few minutes, 30 min, several hours, and several days in the respective tissue groups. Knowledge of these parameters can be helpful in estimating body burden from exposure or vice versa and in planning environmental studies, particularly in setting times to monitor breath in studies of the variation with time of body burden. Improvements in breath methods have made it possible to study short-term peak exposure situations such as filling a gas tank or taking a shower in contaminated water. — *Environ Health Perspect* 104(Suppl 5):861–869 (1996)

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Introduction

Analysis of exhaled breath for volatile organic compounds (VOCs) has a long history in occupational medicine (*1,2*). A number of studies have been undertaken since the 1930s, and the methods are well enough accepted to be put forward as biological equivalents of threshold limit values

(TLVs) for some selected VOCs (*3*). Breath analysis is also well-established in law enforcement with the "breathalyzer" for determining blood alcohol. The precision and dependability of the results allow such evidence to be used in court. Breath measurements have also been undertaken in clinical and psychiatric research (*4*), with results that have had an important impact on later methods employed in environmental studies. However, it is beyond the scope of the present paper to provide a review of these earlier areas. Instead, we focus here on measuring exhaled breath as an aid to our studies of human exposure during ordinary daily activities.

The use of breath analysis in environmental applications is recent and is not yet widespread. Nonetheless, in the short time of its use, a number of discoveries of importance have been made, and the future appears bright for this branch of analysis. In this paper, the basic concepts and methodology of breath analysis are briefly presented. The history of breath analysis as employed in the U.S. Environmental Protection Agency (U.S. EPA) studies (and a few studies sponsored by other organizations) is also summarized. New methods and future directions of research are described.

Basic Concepts

VOCs in inhaled air transfer to the blood at the alveoli. Pharmacokinetic models assume that inhaled air resides in the alveoli for sufficient time to allow VOCs to reach equilibrium with arterial blood. Provided equilibrium is reached, it is governed by the partition coefficient, which determines for each VOC the relative concentration in the blood–breath interface. Partition coefficients have been calculated for about 50 VOCs (*5–8*) using laboratory methods; they have also been validated on human subjects at occupational (ppm) concentrations (*9*), but questions have been raised concerning their applicability at environmental (ppb) concentrations (*10*). In fact, there is some evidence that the blood–breath ratio increases with decreasing concentration. For example, a benzene blood–breath ratio of about 20 was observed for unexposed nurses, compared to a ratio of less than half that for workers exposed to higher concentrations (*11*). Furthermore, the blood flow rate through the alveoli is not linear with breathing rate; therefore, different levels of exertion will result in different levels of partition. All these are complications that must be taken into account when interpreting results of field and chamber studies.

Having a reasonable estimate of the partition coefficient allows us to estimate the arterial blood concentration from the breath measurement. Provided we have some model of the distribution of the chemical in the body, knowing the blood concentration then allows estimation of concentrations in other body tissues.

Pharmacokinetic models are all based ultimately on mass-balance considerations. Differential equations for different compartments (liver, other organs, muscle, fat, etc.) are developed and solved, usually numerically. Historically, a number of simplifying assumptions were made that allowed analytic solution of the equations for certain simple inputs (a single bolus, or a constant exposure at high concentrations); these solutions were generally in the

form of exponential functions with different parameters for each compartment (12, 13). For example, assuming someone without previous exposure to a particular VOC is suddenly exposed to a constant high concentration C_{air}, the alveolar breath concentration C_{ale} is given by (14):

$$C_{ale} = fC_{air}\Sigma a_i[1 - \exp(-t/\tau_i)] \qquad [1]$$

where f = fraction of parent compound exhaled at equilibrium; τ_i = residence time in ith compartment; a_i = fraction of breath concentration contributed by the ith compartment at equilibrium ($t = \infty$); t = time of exposure ($t = 0$ at start of exposure); and $\Sigma a_i = 1$.

One important parameter in these compartmental models is the residence time, τ_i, for the ith compartment. This is the time it takes for the chemical to decline to $1/e$ of its initial concentration in the compartment, assuming all other compartments are at zero concentration. A series of chamber studies sponsored by the U.S. EPA have provided estimates of τ_i for $i = 1 \ldots 4$ for a number of VOCs (14).

A second important parameter in the compartmental models is the fraction, f, of the chemical exhaled under steady-state conditions. This is particularly important for environmental considerations because it may often be the case that persons under normal conditions are at or near equilibrium with their chemical environments; in such a case, multiplying the breath measurement by $1/f$ is quite a good estimate of their long-term average normal exposure. Later we provide estimates of f for a number of chemicals obtained from the U.S. EPA-sponsored field and chamber studies.

Recently, with the advent of more powerful computers, the equations have been solved numerically. This has allowed more realistic consideration of physiological processes and has led to a class of models known as physiologically based pharmacokinetic (PBPK) models (15). Although these models are powerful and have a number of successful applications, they require knowledge of a much larger number of parameters, some of which are difficult to obtain quantitative information on; thus there is some question of how unique their parameter estimates are (16).

Methods

In the mid-1970s, a method of sampling exhaled breath was developed (17,18) using a new sorbent called Tenax (a polymer based on 2,6-diphenyl-p-phenylene oxide). This method was capable of measuring sub-parts per billion levels and represented an improvement in sensitivity over the activated charcoal methods then in use. The method was modified and improved for use in the U.S. EPA-sponsored studies (19–21): The subject inhales pure humidified and charcoal-scrubbed air from a 20-liter Tedlar bag that has previously been filled from a pure air cylinder and then exhales into a second 20-liter Tedlar bag. This bag is then emptied by pumping through a glass cartridge containing 1.5 g Tenax. The entire system was mounted in a van to allow house calls to the participants in the TEAM Studies of 1980–1987. The time required to collect a breath sample was about 5 min. After the first visit to New Jersey in 1981, it was suspected that the Tedlar bags may have been contaminated by exhaust fumes from the van; all later trips incorporated a helium positive-pressure system to bathe the bags while in storage on the van.

An improvement to this method was developed after completing the TEAM Studies and was used in a series of field and chamber studies. The method (22–24) employs a charcoal face mask to allow breathing clean air without the need for a cylinder of clean air and a separate inhalation bag. Several (2–4) breaths are taken through the charcoal filter to flush the alveoli and bronchial tubes of ambient air before collecting the breath sample. The exhalation bag is replaced by an evacuated electropolished 1.8-liter stainless-steel cylinder with a critical orifice (although other suitable collecting devices such as Tenax or other sorbents could also be used). The subject exhales through a 1-m long perfluoroethylene tube, which retains the latter part of the breath (the alveolar portion) for a few seconds during the resting and inhalation parts of the respiration cycle, during which time the alveolar air in the tube is pulled into the cylinder through the critical orifice. The canister collects approximately 98% alveolar air. About 12 breaths are collected over an 80-sec period. The method is readily deployable in the field; electrical power is not needed, and the entire set of equipment fits into a metal carrying case about the size of a suitcase. The cycle time (from beginning to collect one breath sample until readiness to collect another) can be as short as 3 min. A miniature version of the system was made and validated for use in space flight (25).

Recently, a single-breath method has been developed (26). The subject breathes directly into a 1-liter evacuated cylinder through a strawlike attachment; after wasting the first (dead space) portion of the breath, the subject opens the valve on the cylinder to allow collection of the second (alveolar) portion. The cycle time is reduced to approximately 1 min. The new method allows for immediate collection following exposure, thus documenting the maximum breath (and therefore blood) concentration attained during the exposure period. Also, a much more finely detailed picture of the decay curve during the first few minutes of rapid decay can be achieved.

Together with the new sampling method, a three-step sequential analytical approach was developed (27). In the first step, only the carbon dioxide level in the sample is quantified. This allows an estimate of the amount of dead space air included in the sample. Since CO_2 in alveolar air is about 4 to 5%, compared to only 0.035% in outdoor air, a sample including a mixture of alveolar and dead space air will have an intermediate level of CO_2. Determining the CO_2 level allows a quantitative adjustment of the subsequent trace-level determinations to more nearly estimate the alveolar air concentration. Although CO_2 levels vary from person to person according to several factors (such as metabolic rates and the amount of time the breath is held before providing a sample), the CO_2 concentrations should be steady over any given series of breath measurements for a single subject. Deviations from the average established for each person permit correction of the measured VOC levels. In the second step, the sample is analyzed for volatile endogenous compounds such as acetone and isoprene, which are found at levels approaching 1 ppm by volume. This step is also capable of quantitating polar compounds such as methanol, ethanol, dimethyl sulfide, and 2-propanol at parts per billion levels. Finally, in the third step the sample is analyzed in detail for the remainder of the VOCs at subparts per billion levels.

A few years ago, Kelly and co-workers (28) developed a new exhaled breath interface that allows continuous real-time analysis of undiluted breath. The system takes advantage of the high sensitivity and specificity of tandem mass spectrometry (MS-MS) by coupling the exhaled breath inlet to a direct air sampling source [e.g., atmospheric pressure ionization (API) or glow discharge ionization source] and an

MS-MS instrument (e.g., triple-stage quadrupole or ion trap mass spectrometer) (29). The subject inhales clean air from a suitable source and exhales directly into the breath interface. The inlet requires no attention from the subject and provides a constant flow of exhaled air into the mass spectrometer. Trace chemicals in the breath are immediately ionized, and compounds of interest are isolated according to mass. The selected masses are dissociated, and the fragments are identified and quantified. This direct air sampling MS-MS technique thus offers a means of extracting the VOCs directly from the exhaled breath matrix and eliminates the preconcentration step that normally precedes exhaled breath analysis by GC-MS.

The method was tested in pilot studies to measure dimethyl sulfide (which has been shown to be elevated in breath levels of person with liver disease) in breath of healthy people; lactic acid in breath during physical exercise (28); and the elimination of 1,1,1-trichloroethane from breath of a machine shop worker, sampling at 5.5-sec intervals over a 20-min period immediately after exposure (29). The data from the latter experiment were evaluated in terms of a two-compartment model of the body. The residence time for the first compartment was estimated to be 1.2 min and for the second compartment to be 17 min. The method is capable of analyzing both polar and nonpolar organics. Detection limits for certain compounds measured with the API source, such as dimethyl sulfide, are as low as 5 ppt. Most other VOCs exhibit detection limits in the low parts per billion range with either the API/triple quadrupole or glow discharge/ion trap system [(30,31); Gordon et al. unpublished results].

In a recent study designed to validate a PBPK model, Thrall and Kenny (32) developed a real-time technique to quantitatively measure the concentration of exhaled breath VOCs using laboratory rats. Breath samples are collected using a specially designed manifold in which up to four rats can be attached to the manifold via nose-only restraint tubes. The exhaled breath from the rats exits the nose ports and is driven into a common mixing chamber by a continuous flow of supplied breathing air. Samples for analysis by either API/triple quadrupole or glow discharge/ion trap tandem mass spectrometry are continually drawn from the contents of the mixing chamber. Detection limits for the target compound, carbon tetrachloride, are in the range of 2 to 10 ppb.

The highly compact Teledyne 3DQ Discovery ion trap mass spectrometer is expected to form the nucleus of a field-deployable MS/MS system for real-time monitoring of VOCs in breath (and air) (30). The U.S. EPA's Atmospheric Research and Exposure Assessment Laboratory has instituted a cooperative agreement with Battelle Memorial Institute to refine the technique for applications in assessing human exposure.

EPA Field Studies

In the U.S. EPA's TEAM Studies of VOCs in the 1980s (32–42), about 750 persons carried personal monitors for two consecutive 12-hr periods (day and night) to measure their exposure to a target list of 25 to 30 VOCs. The participants were selected according to a strict probability procedure, as in a Gallup poll, so that they actually represented about 750,000 residents of the cities chosen as sites. Each participant provided a breath sample following the 24-hr monitoring period. (In the 1987 TEAM Studies, participants provided samples at the beginning, middle, and end of the 24 hr.)

Several special TEAM studies were also undertaken, most of which included breath sampling. For example, breath and mothers' milk samples were analyzed for the target VOCs in a subsample of 17 nursing mothers selected from the Elizabeth-Bayonne, New Jersey, area (43–45). Breath samples were also collected at home and at work from workers in three dry cleaning shops (46–48).

The suitcase sampler was used (49) to evaluate total benzene body burden resulting from a 20-min shower using gasoline-contaminated groundwater. About 10 breath samples were collected during the 3 hr following the end of exposure.

More recently, the suitcase sampler was used in the Lower Rio Grande Valley Environmental Scoping Study (Buckley et al., unpublished data). However, due partly to using unsuitably high calibration standards, the detection limit was too high (on the order of 1 $\mu g/m^3$) and yielded detectable levels in only 5 (2.6%) of the possible 189 breath samples.

U.S. EPA Chamber Studies

Because of the importance of establishing values for the residence times, τ_i, and the fraction, f, exhaled at equilibrium, a series of chamber studies was sponsored by the U.S. EPA to estimate these values for a representative set of VOCs. The first study (51,52) employed a room-sized chamber at IIT Research Institute in Chicago. Four subjects entered the chamber following exposure over some hours to a mixture of solvents and other products containing the VOCs of interest. Breath samples were collected while subjects were in the chamber during the decay phase of the experiment. The subjects breathed through a port in the chamber to fill a 20-liter Tedlar bag, which was then pulled across a Tenax cartridge for GC-MS analysis. The results included a set of decay curves for a number of chemicals, and initial estimates of f and τ for intermediate compartments such as organs and muscle (i.e., τ_2 and τ_3). However, the very fast initial decay of the chemicals in the blood (τ_1) was not observed in this study because of a delay of about half an hour between the end of the exposure and entry into the chamber.

Later chamber studies (53–60) employed the suitcase sampler developed by Pellizzari. Persons were monitored immediately after leaving commercial establishments with expected high levels of some VOCs and were also exposed for controlled time periods (2, 4, or 10 hr) to high, constant levels of selected VOCs in a chamber. Decay periods of 2, 4, and finally 24 hr were prescribed, during which up to a dozen or so breath samples were taken. This series of studies has resulted in estimates of f and τ_i for four compartments, including blood and fat as well as organs and muscle.

More recently, Buckley et al. (82) studied uptake and decay in breath during inhalation exposure to methyl-*tert*-butyl ether (MTBE). Two persons were exposed to constant levels of MTBE for 1 hr in a room-sized environmental chamber. Breath samples were collected using the suitcase sampler during uptake and decay for 7 hr following exposure.

Results

TEAM Studies were carried out on approximately 350 residents of Elizabeth and Bayonne, New Jersey (1981); 120 residents of Los Angeles, California (1984); 75 residents of Antioch and Pittsburg in Contra Costa County, California (1984); and 75 residents of the Dundalk section of Baltimore, Maryland (1987). Return visits were made to subsets of the New Jersey residents in 1982 and 1983 and to the Los Angeles residents for a second season in 1984 and a winter and summer season in 1987. Smaller studies were also carried out on 25 residents of Devils Lake, North

Table 1. Median daytime personal air and breath concentrations (µg/m³) in selected TEAM study locations.[a]

Chemical	NJ, 1981, fall (n=350) Air	Breath	NJ, 1982, summer (n=160) Air	Breath	NJ, 1983, winter (n=50) Air	Breath	CC, 1984, spring (n=75) Air	Breath	LA, 1984, winter (n=120) Air	Breath	LA, 1984, spring (n=50) Air	Breath	LA, 1987, winter (n=50) Air	Breath	LA, 1987, summer (n=40) Air	Breath	MD, 1987, spring (n=75) Air	Breath
Benzene	12.0	12.0	NM	NM	14.0	5.7	6.3	1.8	15.0	3.1	7.2	4.2	13.2	2.1	7.1	0.9	11.2	2.3
m,p-Xylene	14.0	6.4	13.0	3.2	25.0	3.0	10.0	1.1	23.0	2.3	18.0	1.4	31.4	2.4	16.0	0.6	14.5	1.3
o-Xylene	4.4	2.2	5.1	1.0	9.9	1.0	3.6	0.4	10.0	0.7	4.0	0.5	11.4	0.7	5.0	0.3	3.9	ND
Ethylbenzene	5.0	2.9	4.2	1.7	8.2	1.3	2.9	0.4	8.0	0.8	6.0	0.5	5.9	0.6	3.7	0.2	3.9	0.4
Styrene	2.0	0.8	1.2	0.8	5.8	0.2	0.8	0.5	2.3	0.2	1.5	ND	2.1	ND	1.0	0.2	1.8	0.2
Carbon tetrachloride	1.6	0.7	0.4	0.2	ND	ND	0.8	0.2	0.7	ND	0.7	ND	0.7	ND	0.7	ND	0.9	ND
Chloroform	2.5	1.8	0.8	2.3	2.2	0.1	ND	ND	1.0	ND	0.3	ND	0.4	ND	0.6	ND	3.1	ND
1,1,1-Trichloroethane	11.0	6.6	6.6	5.2	26.0	2.3	5.5	0.1	29.0	6.3	11.0	3.8	14.0	3.8	7.7	2.6	11.5	3.2
Trichloroethylene	2.3	0.9	3.0	0.1	1.7	0.1	0.5	0.2	2.2	ND	1.2	ND	0.7	ND	0.3	ND	1.1	ND
Tetrachloroethylene	8.3	6.8	5.9	4.1	9.7	4.5	2.2	2.0	8.2	5.8	3.4	4.0	5.3	4.0	2.3	1.8	2.4	2.0
m,p-Dichlorobenzene	3.4	1.3	2.3	1.3	5.8	1.2	0.9	0.9	2.2	0.5	0.9	0.6	2.4	1.0	1.0	0.3	2.5	ND
a-Pinene	NM	NM	NM	NM	NM	NM	1.0	0.3	1.9	0.9	1.6	0.9	2.8	1.1	1.2	ND	2.6	1.3
d-Limonene	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	25.3	22.2	4.3	14.4	28.9	19.0
Octane	NM	NM	NM	NM	NM	NM	2.3	0.5	4.1	0.5	3.2	0.8	4.0	0.8	2.6	ND	3.4	0.6
Nonane	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	3.2	0.3	2.3	ND	2.8	0.5
Decane	NM	NM	NM	NM	NM	NM	1.0	0.7	2.2	0.3	1.8	0.3	3.0	0.4	2.0	ND	3.9	0.5
Undecane	NM	NM	NM	NM	NM	NM	1.3	0.7	2.8	0.4	1.3	0.3	3.2	0.4	1.9	ND	3.4	0.4
Dodecane	NM	NM	NM	NM	NM	NM	1.0	0.2	1.6	ND	0.7	0.3	2.2	0.3	1.1	ND	2.3	ND

Abbreviations: NJ, Elizabeth and Bayonne, NJ; CO, Contra Costa County (Antioch and Pittsburg, CA); LA, Los Angeles, CA; MD, Baltimore, MD. NM, not measured; ND, not detected (detection limit varies by chemical and by sample volume; range is usually 0.1–0.3 µg/m³). [a]All values are population-weighted values and refer to the estimated median for the target population, based on probability of selection of the participant.

Dakota, and Greensboro, North Carolina, in 1982, and 11 residents of Elizabeth, New Jersey in 1987, but results from these smaller studies are not reported here.

Daytime median 12-hr average personal exposures and subsequent breath concentrations are provided in Table 1 for 18 prevalent chemicals from four chemical classes. Because of the possible contamination of the Tedlar bags by van exhaust fumes during the first (1981) New Jersey trip, the breath values for gasoline-related VOCs such as the aromatic compounds may be erroneously high for this first visit. Also, during the second (summer 1982) trip to New Jersey, contamination of the Tenax cartridges during storage in a hotel that had been recently renovated may have affected the results for both air and breath values; blank values were unusually high and variable, and thus the estimated values are uncertain, although the direction of error cannot be determined.

Because all residents were visited at home in the evening to obtain their breath samples, and because more than 75% of them had been home for a number of hours before the sample was taken, it is likely that most were being sampled under normal or typical conditions. This makes it probable that the blood and breath concentrations for many of the residents were close to equilibrium with their surroundings. Even for those not close to equilibrium, it seems likely that for most chemicals roughly equal numbers of persons were either above or below their equilibrium breath concentrations. By this reasoning, the ratio of the median values for the breath and personal air concentrations of the participants should be close to the equilibrium value of f. The chamber studies provide an independent estimate of f, although for a much smaller population. The estimates of f obtained from the field and chamber studies are compared in Table 2.

Perhaps the most striking evidence of the importance of making breath measurements was the discovery that the single most important source of exposure to both benzene and styrene for some 50 million Americans is active smoking. The personal monitor detected a modest increase of about 50% in personal air exposures, but the breath values documented a 6- to 10-fold increase in benzene and styrene concentrations in the breath of smokers (Figure 1).

In the benzene shower study described above, the decay curve was not at all similar to the decay curves previously noted for benzene and other aromatics, suggesting that a second pathway (presumably

Table 2. Observed breath–air ratios versus equilibrium values of f calculated from chamber studies using linear model.
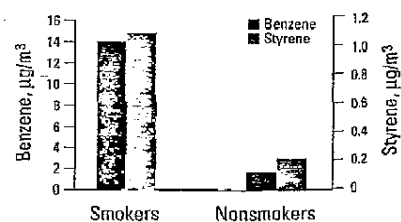
Chemical	Calculated values of f[a] Mean	SD	Observed median breath/air ratios[b] (322 nonsmokers) Mean	SD
Aromatics				
p-Xylene	0.08	0.02	0.08	0.04
o-Xylene	0.06	0.02	0.08	0.02
Ethylbenzene	0.08	0.01	0.10	0.03
Benzene	NM		0.17	0.06
Styrene	NM		0.20	0.11
Toluene	0.07	0.02	NM	
Chlorinated				
Trichloroethylene	0.22	0.05	0.19	0.07
1,1,1-Trichloroethane	0.88	0.07	0.21	0.16
Tetrachloroethylene	NM		0.75	0.19
Carbon tetrachloride	NM		0.26	0.14
p-Dichlorobenzene	NM		0.44	0.18
Dichloromethane	0.18	0.07	NM	

Abbreviations: NM, not measured; SD, standard deviation. [a]From Wallace et al. (81). [b]From Wallace et al. (39).

Figure 1. Benzene and styrene concentrations in exhaled breath of smokers and nonsmokers. Data from the U.S. EPA TEAM Studies of 200 smokers and 300 nonsmokers (39).

Table 3. Median residence times (range across five subjects), τ_j (hr) in four compartments.

Chemical	First	Second	Third	Fourth
Aromatics				
Toluene	0.06 (0.05–1.0)	0.64 (0.41–2.2)	5.3 (3.7–17)	84 (41–105)
p-Xylene	0.10 (0.08–0.22)	0.59 (0.33–1.8)	4.2 (3.4–6.2)	51 (29–131)
o-Xylene	0.15 (0.09–0.18)	1.9 (0.15–3.5)	3.7 (2.7–5.9)	64 (29–185)
Ethylbenzene	0.07 (0.07–0.18)	0.58 (0.19–3.2)	3.3 (2.6–7.4)	90 (25–115)
Aliphatics				
Hexane	0.07 (0.04–0.15)	0.38 (0.23–0.67)	4.7 (3.1–5.3)	56 (45–118)
Decane	0.05 (0.04–0.06)	0.27 (0.07–1.5)	2.0 (1.9–7.2)	63 (25–71)
Chlorinated				
1,1,1-Trichloroethane	0.15 (0.08–0.20)	0.68 (0.47–2.2)	4.8 (3.9–17)	29 (25–49)
Trichloroethylene	0.09 (0.06–0.11)	0.55 (0.34–1.5)	4.2 (3.9–6.6)	44 (35–196)
Dichloromethane	0.19 (0.09–0.28)	0.53 (0.38–2.0)	4.7 (3.0–6.9)	61 (27–312)

Data from Wallace et al. [81].

dermal) was contributing to the uptake and decay of benzene. By assuming an expected decay due to inhalation only and subtracting the expected breath levels from the observed values, Buckley et al. (unpublished data) derived an estimate of the contribution of dermal absorption to total body burden.

The chamber studies discussed above provide estimates (Table 3) of the residence times, τ_j, for nine VOCs drawn from three classes: aliphatic, aromatic, and halogenated hydrocarbons. Using the average values of f and τ_j for each of these three classes, the observed breath concentrations during the postexposure period for all five subjects during the chamber studies can generally be predicted to within 30%, except at the very end of the decay curve, when concentrations approach the detection limit (Figure 2).

The more recent chamber study of MTBE mentioned above resulted in a three-compartment model fit to MTBE breath decay (Figure 3) yielding residence times for the first compartment of 2 to 5 min, for the second compartment of 20 to 50 min, and for the third compartment of 5 to 12 hr. Thus, the residence times for MTBE appear to be roughly similar to those calculated for other (nonpolar) VOCs. Values of f for a 226-lb male and a 147-lb female were calculated to be 0.46 and 0.6, respectively. The blood–breath

partition coefficient was calculated to be in the range of 15 to 20, based on simultaneous blood measurements in both subjects; however, the likelihood that MTBE, a polar chemical, might be absorbed in the mucous membranes, resulting in larger differences than usual between the measured exhaled breath and the alveolar concentration, made this estimate uncertain.

Discussion

The existence of the large (800-person) data set of personal exposures and breath concentrations from the TEAM Studies allows us to investigate the relationship between exposure and body burden for the approximately 18 prevalent target VOCs. The fairly strong relationships that were found (correlation coefficients between breath and previous air exposure of about 0.3 to 0.4, significant at $p < 0.0001$ for the most part) indicate that a breath measurement alone can provide some information about past exposure as well as current body burden. Although this exposure–body burden relationship was the prime reason for collecting the breath measurements, there was a second reason: to detect whether unmeasured routes of exposure were contributing to body burden. In the TEAM Studies, personal air and drinking water were monitored, but food was not, nor was mainstream cigarette smoke. If either food or active smoking was an important route for any of the target VOCs, that VOC might show up in the breath at a higher level than expected. In fact, this was the way in which some of the most important
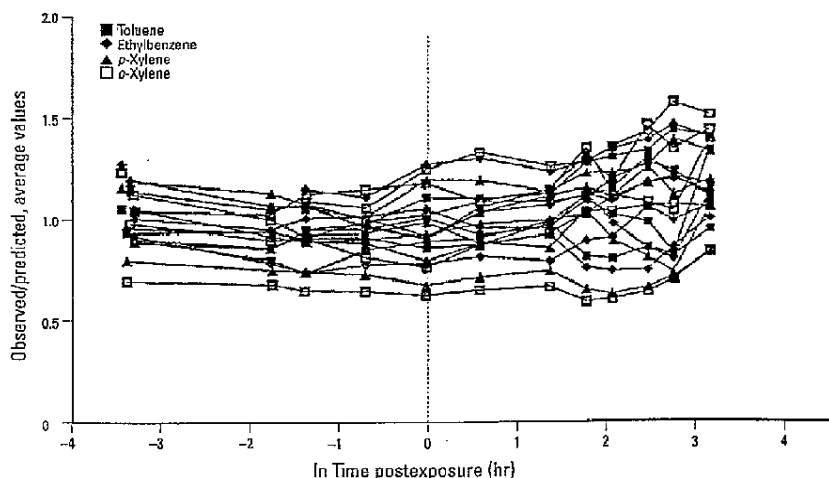
Figure 2. Residual errors from a four-compartment fit to observed breath concentrations of four aromatic chemicals in a chamber study of five subjects. Subjects were exposed for 10 hr to a constant concentration of toluene, ethylbenzene, p-xylene, and o-xylene. The fit is to the subsequent 24-hr decay while the subjects were in a clean environment. Only one set of parameters (the residence time for each of the four compartments averaged over all four compounds and all five subjects) was used in the model. Virtually all observed points are within 30% of the predicted values except for the final measurements, which are close to the detection limit of the method [81].
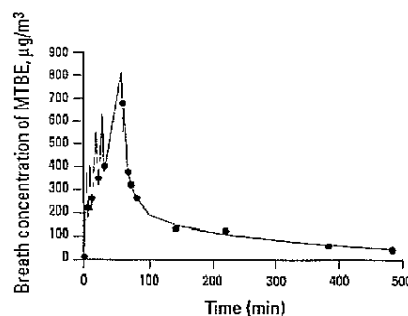
Figure 3. A three-compartment fit to the observed breath values of methyl-*tert*-butyl ether (MTBE) for one subject during a 1-hr exposure followed by a 7-hr decay period. The residence times are on the order of 2 min, 17 min, and 4.5 hr for the first three compartments. The "sawtooth" portion of the curve during the exposure period results from the subject breathing pure air for 2 min at a time while providing a breath sample (Buckley TJ. in preparation).

TEAM Study findings were first discerned—smokers had 6 to 10 times the level of benzene and styrene in their breath as nonsmokers, immediately pinpointing active smoking as the single most important source of exposure to these two chemicals for about 50 million Americans. A second interesting result was the lack of a detectable relationship between any of the foods reported eaten and resulting breath concentrations of benzene and most of the other VOCs. In view of earlier studies reporting benzene at high concentrations in foods (particularly eggs), this was a negative finding of considerable interest. Since then, other investigators have occasionally found halocarbons in food (61,62) but have still not found benzene (63) in environmentally significant quantities in a large number of foods.

It is relevant to note that breath sampling was initially selected for the TEAM Studies in preference to blood sampling for two major reasons: a) Breath sampling is more sensitive than blood sampling. A typical limit of detection for many VOCs in breath is 0.2 μg/m³. Depending on the partition coefficient, this corresponds to part-per-trillion levels in blood, which are extremely difficult to quantitate adequately. b) Breath sampling is more acceptable to people than blood sampling. The method is noninvasive and easily mastered by young and old. For population-based studies such as TEAM, it is particularly important to achieve a high response rate, and blood sampling would no doubt have depressed the response rates of 50 to 60% normally achieved in the TEAM Studies.

Having trustworthy estimates of the main breath parameters (f and τ) is important in several ways. For example, in designing chamber studies, it is important the collection of the breath samples to gain maximum efficiency in defining the decay curve. Typically, two measurements bracketing each expected residence time, τ_i, are about the minimum required to delineate the decay curve adequately. Also, knowing the expected value of f helps to determine the initial exposure concentration required to assure detectable concentrations at the end of the decay period.

The values of f estimated from the field studies are generally similar to the values determined from the chamber studies; therefore it appears that they can be used with some confidence to estimate the relationship between airborne exposure and resulting body burden. In two cases

(chloroform and limonene) f exceeds 1. Of course, the reason for this is that both chemicals have major routes of exposure other than the air. Chloroform is contained in drinking water, soft drinks, and dairy products (33,50,51); limonene in citrus fruits, soft drinks, and other foods. However, it appears that for all the other target chemicals, air provides 95 to 100% of the total exposure.

The residence times are quite similar from one chemical to another. It appears that for all these VOCs, an initial residence time on the order of 3 min, and a secondary one on the order of 30 min, is not a bad approximation. Fewer data are available for the third and fourth residence times, due partly to the difficulty of keeping subjects for 24 hr in a completely clean background. Thus, the residence time estimates for muscle and fat tissues of about 3 hr and about 3 days, respectively, are more uncertain than for the vessel-rich tissues.

An important use of breath sampling is in estimating dermal absorption of VOCs. In one study, breath samples were collected from volunteers who took showers with and without rubber suits to isolate the contributions of inhalation and dermal absorption of chloroform (64,65). The breath levels were about twice as high in persons who showered without the rubber suits, suggesting that dermal absorption accounted for about half of the total chloroform uptake during the showers.

More recently, a study of swimmers at an indoor pool in which the chloroform content of the water was regulated showed that breath concentrations after normal swimming were about 4 times higher than those after swimming with a scuba tank supplying pure air (66). The authors concluded that dermal uptake was thus responsible for about 25% of the total chloroform uptake during swimming. [The difference between their results and the earlier ones from the shower studies (64,65) was attributed to the hotter temperature of the shower water and possibly the permeability-affecting properties of the soap and shampoo used in the shower.] Other studies of chloroform exposure in showers or swimming pools have also utilized breath samples as an estimate of combined inhalation and dermal exposure (67–70).

An interesting recent hypothesis is that exhaled breath may not only reflect exposure but also cause it. Using data from the TEAM Study of dry cleaners mentioned earlier, which found breath values of 10,000 to 25,000 μg/m³ in the workers

and elevated home air values of about 100 μg/m³, Thompson and Evans (71) used a PBPK model to estimate that all or a portion of the increased home air levels could have been introduced from the workers' breath.

Another area where breath sampling could be useful is in relating compounds in breath to disease, perhaps as early warning markers for lung cancer (72,73). Related studies have identified a marker of active smoking in smokers' breath: 2,5-dimethylfuran (74,75). This marker may even be useful in identifying exposure to environmental tobacco smoke (76). Other diseases for which breath sampling has been used as a diagnostic tool include malabsorption syndrome and pancreatic damage, both of which result in increased amounts of hydrogen in breath following a dose of certain sugars (77), and peptic ulcers and chronic gastritis due to *Helicobacter pylori* infections, which can create CO_2 in the breath by using the urease enzyme found in these bacteria to metabolize urea, which is otherwise not metabolized by the stomach (4). Breath sampling has also been used in identifying exposure to VOCs in confined spaces, such as submarines (78).

Unfortunately, few data are available on simultaneous measurements of blood and breath on the same subjects at environmental levels of exposure; such data would be extremely useful in determining how well the partition coefficients obtained in chamber studies and occupational (high-exposure) situations apply to low-exposure environmental conditions. Some studies (10,11) suggest that blood–breath ratios at low concentrations may be 2 to 3 times the ratios at high concentrations. A possible explanation for this phenomenon is the sequestering of a portion of the inhaled chemical by proteins in the blood (79). If the capacity of the proteins is relatively small, they would become saturated as concentrations increased, and the laboratory values of the partition coefficient would be approached.

In the absence of such simultaneous blood and breath measurements at environmental levels of exposure, it is possible to arrive at a rough estimate of blood–breath ratios at low levels by comparing the TEAM Study results on breath levels of representative subpopulations with the National Health and Nutrition Examination Survey study results on blood levels of a nationwide sample (80). Provided that the two populations are roughly comparable, this comparison

Table 4. Blood–breath ratios averaged over all TEAM sites.

Chemical	Percentile		
	50th	Mean	95th
Chloroform	21	17	12
1,1,1-Trichloroethane	23	10	7
Trichloroethylene	12	8	3
Tetrachloroethylene	10	10	5
Benzene	11	10	8
Styrene	80	52	29
Ethylbenzene	40	28	19
o-Xylene	76	42	38
m,p-Xylene	49	43	29
m,p-Dichlorobenzene	272	275	220

Breath values divided by 0.7 to allow for dead space. Breath values from TEAM Studies (35–37,40 42). Blood values from NHANES Study (80).

(Table 4) suggests that the blood–breath ratio increases at the mean compared to the 95th percentile; the increase is greater at lower percentiles, such as the median.

Future Directions

The two newer methods of breath sampling, the suitcase sampler and single-breath method discussed above, provide excellent capabilities for exploring exposures occurring in all types of locations, from beauty salons to gas stations to swimming pools. In fact, all three of these locations have been studied in recent years. The portability of the methods allows samples to be taken during or immediately after the exposures, thus getting the most accurate estimation of the peak levels caused by the exposure. The single-breath method has the further advantage of being capable of collecting multiple samples during the first half hour either of uptake during exposure or of decay following exposure, thereby obtaining an estimate of the half-lives in the first two compartments. One drawback to these two methods and to the real-time MS/MS methods discussed above is a limit of detection in the low parts per billion range that is of the same order of magnitude as typical breath concentrations for many VOCs of interest. However, a number of situations involving slightly elevated environmental exposures are open to investigation using the present methods. Moreover, work currently in progress at Battelle (and elsewhere) is designed to improve the sensitivity of this approach for breath analysis applications by at least an order of magnitude. If successful, this would open up to investigation a significant fraction of the environmental exposures of interest.

We conclude that breath sampling is a fertile and developing scientific discipline with much promise for providing useful data on scores or hundreds of VOCs of present or future interest.

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